



Antihypertensive drugs

Normal hypertension = 120/80 mmHg

Uncomplicated hypertension, slight elevation = 120-139/80-89 mmHg, and it is treated with thiazide (diuretic) only, not Lasix, because thiazide reduce blood pressure about 10mmHg.

Three stages of hypertension:

- 1) blood pressure more than 140/90 mmHg
- 2) blood pressure more than 160/95 mmHg
- 3) blood pressure more than 180/100 mmHg

There is a special case in dental case called uncomplicated hypertension, the rise of pressure is simple here, when it is 120-139/80-89 mmHg, we treat this patient with thiazide only, no other drug Or give him advice like bed rest, change in life style, avoiding salts and cholesterol, mild sport, walking, avoid stress and emotional tension....

What's the meaning of hypertension?

هو التأثير بسعة شريان الدم من الكبيرة المتوسعة الى الصغيرة المتضيقة مما يؤدي الى قوة دفع وارتفاع ضغط الدم

There are two types of hypertension: primary hypertension, secondary hypertension.

More than 95% of patients or population suffer from primary hypertension but the cause is unknown, maybe cause of other disease, maybe pt. has D.M and this causes hypertension or the pt. has hyperlipidemia converted to hypertension, or kidney disease converted to hypertension. That means converted from other diseases but the cause is unknown.

There may be signs of primary hypertension or factors:

1. Age, older people are more vulnerable to have AHT.

2. Sex, males have more risk to get AHT than females.
3. Race, black people have higher risk to have AHT, because salts are retained in their body.
4. Cholesterol.
5. Smoking.
6. Alcohol.
7. Nervousness.

Secondary hypertension is seen in less than 5% of pt., factors are: some drugs like non-steroidal drugs (increase BP), steroidal drugs (increase BP), kidney disease (increase BP), D.M. (increase BP), hyperlipidemia (increase BP), so it can be drug induced or due to other diseases.

ANTIHYPERTENSIVE DRUGS

Drugs that reduce blood pressure in arterial hypertension.

Ch. of these drugs: safe, insure clinical uses, available in pharmacy, suitable by all pt. in hospital and cheaper.

Hypertension is a very frequent disease >140/90 mmHg and majority of cases are primary AHT 95%. It has multi-factorial causes: inheritance, stress, environmental and dietary factors.

ACE inhibitor drugs inhibit enzyme kinase 2 (angiotensin converting enzyme), increase bradykinin to decrease BP. Losartan block subtype receptor angiotensin receptor blocker drug. Vasodilator drugs decrease after-load and decrease preload to decrease BP.

Arterial pressure is determined by cardiac output (CO) and peripheral resistance (PR)
When increase CO → increase stroke volume, increase heart rate, increase myocardial contraction, increase venous return blood volume and venous capacitance.

When increase PR → increase arteriolar tone, increase alpha and beta receptors, increase calcium ions.

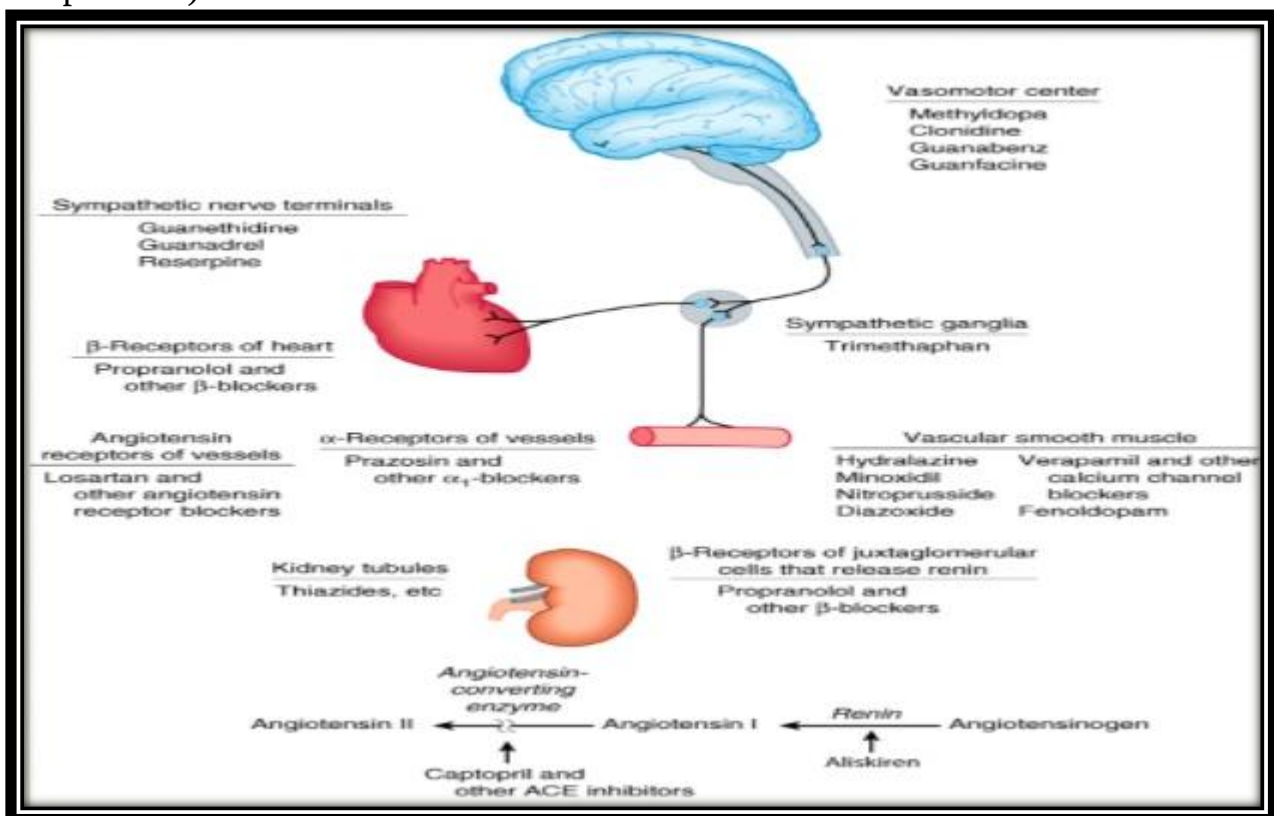
If blood volume increase, cardiac output will be increased. And increase in calcium leads to increased PR causing contraction.

Advices should be given to pt. With AHT:

1. Education of pt. for good compliance, life style, which means relaxation, exercise and get bed rest.
2. Low salt and fat intake
3. Moderate physical activity.
4. No smoking, no alcohol.
5. Avoid stress and emotional tension.
6. Adequate treatment of concomitant disease, like D.M., hyperlipidemia and thyroid disturbance.

CLASSIFICATION OF ANTIHYPERTENSIVE DRUGS:

1. DIURETICS, drugs that eliminate sodium and water from the body, decrease blood volume, decrease BP (chlorthiazide, furosemide, spironolactone or aldactone)
2. ANGIOTENSIN CONVERTING ENZYME INHIBITORS, the drug of choice in hypertension in all grades of hypertension and Reno vascular disease (captopril, enalapril, Lisinopril)
3. ANGIOTENSIN RECEPTOR BLOCKER DRUGS, losartan, saralazin
4. CENTRAL SYMPATOLYTICS, produce euphoria in CNS (alpha-methyldopa, clonidine)
5. BETA ADRENERGIC BLOCKER DRUGS, drugs that block beta receptors in the nervous system (propranolol, atenolol, metoprolol)
6. ALPHA ADRENERGIC BLOCKERS, drugs that block alpha adrenergic receptors in central nervous system (prazosin, terazosin, doxazosin)
7. CALCIUM CHANNEL BLOCKERS, drugs that block or decrease calcium ions to prevent smooth muscle contraction to produce relaxation and decrease BP (nifedipine, diltiazem, nitrendipine)
8. VASODILATORS, the second choice drugs for hypertension (hydralazine, sodium nitroprusside)



Site of action of antihypertensive drugs,

In the brain, kidneys, blood vessel or heart (alpha receptors and beta 1 receptors). Hypertension produces tissue damage in the eyes, brain, kidneys, and heart causing arteriosclerosis. cholesterol is the most important cause of hypertension.

Site of action of Methyldopa and clonidine is the brain, if the pt. has brain hypertension, we give him one of these drugs. If malignant hypertension we give

sodium nitroprusside or hydralazine but we can't give methyldopa because this drug is for chronic hypertension not acute or malignant so we think of drug that penetrate the blood brain barrier, decrease noradrenalin and decrease blood pressure, like trimethaphan, it is used in emergency hypertension, brain hypertension, dentistry, surgery, when BP greatly increases and there is bleeding.

Blood vessels, including arteries, veins and capillaries. When the artery extends this leads to increase BP (vasoconstriction) and when there is relaxation, BP decreases.

DIURETIC DRUGS:

First, Thiazide.

Second, high ceiling diuretics including furosemide.

Third, potassium sparing diuretics including aldactone or spironolactone

Thiazides like hydrochlorothiazide, no change in BP in normotensive, in monotherapy or associated with other antihypertensive drugs, its antihypertensive action is mild and slow, decrease BP in about 10 mmHg during the period 2-4 weeks, long treatment decreases PR, increases plasma renin activity. The proposed mechanism of thiazide is decrease extracellular fluids, decrease sodium ions as a result decrease BP in intracellular fluids thiazide reduce responsiveness of vascular smooth muscles to vasoconstrictor stimuli like noradrenalin or angiotensin 2.

High ceiling diuretics, furosemide or Lasix, weaker than thiazide as antihypertensive effect because the thiazide decrease BP 10 mmHg but Lasix or furosemide doesn't decrease BP 10 mmHg. So, as antihypertensive thiazide is more than furosemide but as a diuresis effect Lasix cause over diuresis and thiazide is less.

Toxicity: hypokalemia (reduce potassium), carbohydrate intolerance, hyperuricemia (increase uric acid).

Clinical uses: chronic renal failure, refractory congestive heart failure, resistance to thiazide we choose another drug like furosemide.

Potassium sparing diuretics, spironolactone (aldactone) a drug that blocks aldosterone receptors leading to decreased aldosterone release, no change in fluids but increase potassium (hyperkalemia), spironolactone is used in primary and secondary hyperaldosteronism, in primary hyperaldosteronism like hypertension we give aldactone to block aldosterone receptor, in secondary hyperaldosteronism like CHF, Crohn disease, we can give aldactone but it has many adverse reaction, for example, gynecomastia in males and excessive hair in females.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS:

Captopril, enalapril,

They inhibit angiotensin converting enzyme kinase II to increase bradykinin, in kidney decrease sodium and water retention, in adrenal cortex decreases aldosterone release, in blood vessels cause of vasodilatation, decrease blood volume, decrease PR,

decrease BP. For example, captopril decreases PR, decrease systolic and diastolic BP, little effect in normotensive, captopril produce dilatation of renal vessels that's why we give it to pt. with kidney disease, because it leads to dilatation of renal vessels. Mechanism of action of captopril, decrease angiotensin 2, by each feedback mechanism? increase plasma renin activity, increase angiotensin 1 but decrease or block angiotensin 2.

Pharmacokinetics: oral absorption 70%, food reduce absorption, don't give captopril with food, it decreases its bioavailability, abolish effect.

Toxicity: hyperkalemia (increase in potassium), persistent cough.

Contraindication: in case of bilateral renal artery stenosis, captopril is not used. If pt. doesn't have bilateral renal artery stenosis, we use ACE inhibitor drugs like captopril with thiazide drug. In pt. with renal impairment with hypertension, we give captopril with thiazide. Sometimes when we use captopril with thiazide there is no change in BP, no decrease in BP, you should stop diuretic drug and decrease the dose of captopril if it was 25 mg we use only 12.5 mg orally, if BP reduce here, you should increase the dose of captopril gradually to 25 mg.

ANGIOTENSIN RECEPTOR BLOCKER DRUGS:

Drugs that block the receptor of angiotensin, losartan (oral) and saralazin (iv injection), losartan is non peptide given orally because if the drug is peptide we give it iv and if it is non peptide we give it orally. Losartan has less oral absorption, less toxicity. Sometimes if pt. come to your clinic suffering from hypertension with dry cough, treat him with losartan not captopril because losartan doesn't produce cough as a side effect. It is given in mild and moderated hypertension and decrease diastolic hypertension.

SYMPATHOLYTIC AGENTS:

2 drugs are still used up to now, clonidine and methyldopa. Methyldopa stimulation of central alpha adrenergic receptors by metabolize alpha methyl noradrenaline where inhibit sympathetic outflow to the heart, to the kidneys and peripheral vasculature. Alpha methyl noradrenaline is formed in the brain from methyldopa which acts on central alpha receptors to decrease sympathetic outflow to decrease PR more than heart rate and CO. Methyldopa acts on the neuron in vasomotor center more than clonidine.

Alpha methyldopa is precursor of dopamine and noradrenaline, reduce PR more than the heart rate and CO, alpha-methyldopa acts on neuron in vasomotor center more than clonidine decreases noradrenaline synthesis and forms the false transmitter for methyl-noradrenaline in periphery.

Clonidine is opposite, doesn't cause stimulation of alpha 2 receptors, partial agonist on alpha 2 receptors with high affinity and intrinsic activity on alpha 2 receptors, decrease sympathetic outflow to decrease blood pressure, cause of bradycardia, as a result of bradycardia it will make increase in vagal tone, increase vagal activity. Why increase

in vagal activity? due to decreased BP, decrease sympathetic outflow, cause of bradycardia and this is the main cause of increase vagal tone and increase vagal activity but clonidine only drug used in hypotension with migraine.

Pharmacokinetics: good oral absorption

Toxicity of methyldopa: causes sedation, dryness, coombs test, lupus erythematosus, diarrhea, hemoglobulinemia, gradual thrombocytopenia. Clonidine causes drowsiness, bradycardia, dry mucosa. From this side effects of methyldopa and clonidine, the conclusion is, if the pt. come to hospital we don't give him clonidine if he is young, if the pt. Is old (over 60 or 55 years) we can't give her clonidine, we give her methyldopa because it fits old people, it decreases sexual activity (this is a problem if pt. is young) and it increases renal flow, increase kidney function (which is usually decreased in old people), increase kidney secretion and causes sedation.

Imipramine, tofranil (antidepressant) and chlorpromazine, largactil (used for schizophrenia), these two drugs abolish effect of action of methyldopa because they act on the site of action of methyldopa, one causes stimulation of alpha receptors and the other cause inhibition of alpha receptors. Decrease absorption, decrease effect, that's why we don't give imipramine or chlorpromazine with methyldopa or clonidine because they abolish effect.

BETA ADRENERGIC BLOCKERS:

They are two subtype groups: selective and non selective beta 1 blocker.

Non selective, including propranolol, sotalol, timolol.

Propranolol is used in hypertension, angina and arrhythmias.

Sotalol is used in hypertension and arrhythmias.

Timolol is used in hypertension and glaucoma, topical eye drops, decrease BP in pt. with glaucoma (glaucoma is increase outflow pressure in eye, increase tension in eye, increase osmotic pressure in the eyes, increase sodium and water retention in the eyes, so increase intra-ocular pressure).

Selective beta 1 blockers, metoprolol is used in pt. with hypertension and D.M., propranolol is not used in this case

Atenolol is common drug used in hypertension with angina.

Acebutolol for hypertension and arrhythmia.

Mild potency, minor effect in normotensive people. For example, propranolol, Inderal slow but sustained action. The first drug discovered in this group is propranolol in 1958, decreases PR, decreases CO, decreases systolic and diastolic pressure, propranolol is the drug of choice in elevated diastolic pressure, after it captopril then vasodilator drugs. Other drugs can decrease systolic pressure, systolic can decrease easy, it can be decreased by using garlic...

But diastolic is difficult to decrease, it takes long period of medical treatment.

In beta blockers we must adjust the dose due to their wide side effects, propranolol decreases PR, decreases CO, decreases HR, decreases O₂ consumption, velocity of

conduction is reduced in atria due to decrease sympathetic activity, AV node and ventricles, refractory period increases in AV node. First block beta receptors then increase arterial pressure. Propranolol decreases automatism when it is decreased it decreases arrhythmias, decreases conduction, decreases heart rate, decreases frequency (because propranolol decreases severity and frequency of the attacks, decreases HR). Chronic use of propranolol lowers PR, diastolic and systolic pressure due to cardiac depression, decrease renin and norepinephrine release.

Pharmacokinetics: oral absorption, longer effect

Toxicity: - bronchial spasm (due to block beta 2 receptors) so contraindicated in pt. with asthma.

- Paradoxical effect: rebound hypertension on sudden withdrawal, don't stop beta blockers it must be gradually, decrease the dose, 1st week, 40 mg or 80 mg, 2nd week, 30 mg, 3rd week, 20 mg.....10 mg daily for a week. If stopped suddenly, instead of blocking beta receptors it will stimulate alpha receptors, decrease depression, increase BP.
- Worsening of peripheral vascular disease, why? Decrease O₂ in the circulation.
- Carbohydrate intolerance by propranolol, why? Because it blocks the store of glucose in the liver, reduce insulin release, so **contraindicated** in pt. with diabetes, (if necessary, use metoprolol, selective beta₁ blocker, if not available in the pharmacy, we use captopril (safe in D.M. Pt.) also if there is kidney problem with hypertension also safe to use captopril (because it is the drug of choice of all grades of hypertension and Reno vascular disease).

ALPHA ADRENERGIC BLOCKER DRUGS:

Prazosin, terazosin, doxazosin

Competitive antagonist of alpha 1, alpha 2 adrenoreceptors. Rapid effect to decrease BP, strong vasodilatation to decrease BP rapidly, so these drugs are very dangerous. May cause fainting, lipothermia, so we don't give this drug unless pt. is in bed rest or before sleeping.

Hemodynamic effects are similar to that of vasodilators, decrease PR, slight decrease in CO, but decrease BP, tolerance and increase in plasma renin activity because increase Na⁺ and water retention.

Pharmacokinetics: oral dose produces peak to decrease BP, first dose effect: fainting, lipothermia

Prazosin is contraindicated in monotherapy use because gradually develop tolerance.

Advantages: 1. decrease LDL cholesterol.

2. Old people feel like a needle pricking in their legs due to arteriolar constriction, Raynaud syndrome, so alpha blocker drugs treat these patients, if not available choose nifedipine a calcium channel blocker.

3. People who chew qat, qat contains pesticides, cause cancer, these pesticides are collected in places of urine excretion, in bladder, so it can cause prostatic hypertrophy or cancer, bladder has alpha receptors, and when pesticides are collected they effect alpha receptor in the trigon zone in bladder, when this happens there will be anuria especially in old people, so these patients must have surgery but if they don't want we give them alpha receptor blocker drugs (block alpha trigon zone receptor in the bladder this leads to increase in kidney secretion and fluids excretion.

CALCIUM CHANNAL BLOCKER DRUGS:

Diltiazem, nifedipine, verapamil

Diltiazem and verapamil produce peripheral vasodilatation, so suitable with pt. with simple hypertension

Nifedipine is used only in malignant hypertension 10 mg (2 capsules, 5mg each) of nifedipine chewing (open capsule and chew the granules inside) this decrease BP rapidly. In case of chronic hypertension, we don't use nifedipine, instead we use verapamil and diltiazem, also use in pt. with hypertension and arrhythmias or hypertension with angina. But nifedipine is given only in malignant hypertension, why? Because it is associated with risk of infarction. if we give injection of nifedipine, and monitor its effect on computer program, we note that the peak of nifedipine effect is very high show risk of MI.

They reduce PR without affecting CO (in therapeutic dose) in comparison between nifedipine, diltiazem and verapamil effect, diltiazem produce smooth muscle relaxation, used in pt. wit contraction and hypertension. But verapamil is better because it produces double time relaxation of smooth muscles than diltiazem and nifedipine produce 3 times smooth muscle relaxation than verapamil. In the comparison between them, nifedipine increases the heart rate, verapamil and diltiazem decrease heart rate. Nifedipine causes tachycardia, verapamil and diltiazem cause bradycardia. If pt. is operating and has tachycardia, we don't give him pethidine because it produces tachycardia instead, we give him morphine because it produces bradycardia and if pt. Has bradycardia we give him pethidine.

These calcium channel blocker drugs decrease calcium and at the same time produce tachycardia or bradycardia, so we use them according to the pt., if he has tachycardia, we give him diltiazem or verapamil, and if he has bradycardia we give nifedipine. Nifedipine is used as anti-angina and not used in arrhythmias but diltiazem and verapamil are used in hypertension, angina and arrhythmia.

VASODILATOR DRUGS:

Hydralazine and sodium nitroprusside.

Drugs used in sever hypertension, used in malignant hypertension. They are very important life saving drugs, to decrease the after load, to decrease BP rapidly we use

hydralazine because it has effect on arteries only, produce arteriolar dilatation, either small or large → decrease after load, decrease BP rapidly. Sodium nitroprusside produce arteriolar dilatation → decrease after load, and produce venous dilatation → decrease preload, decrease BP.

In the comparison between them in kidney disease or impairment, we give this medication but it is preferred to give hydralazine because it directly increases nitric oxide NO, produce renal dilatation, increase renal blood flow, increase renal function, increase renal secretion so improve renal condition, whereas, sodium nitroprusside indirectly increase NO, produce renal vasodilatation, increase kidney function, increase renal blood flow, improve pt. condition. If these drugs are not available and we want to increase NO directly, we give nifedipine and it will directly increase NO to produce renal vasodilation, increase kidney function.

Vasodilators decrease PR and great reduction in diastolic blood pressure.

There are three important mechanism of action of vasodilator drugs:

1. Increase sympathetic activity due to increase sodium and water retention → increase plasma renin activity.
2. Produce reflex compensatory mechanism → tachycardia, associated with diuretics and beta blockers.
3. Causes relaxation by increasing NO, increasing cGMP, and decrease calcium influx → smooth muscle relaxation → decrease BP.

Pharmacokinetics: hydralazine, slow absorption. Sodium nitroprusside, only intravenous infusion, rapid after stop.

Toxicity of hydralazine: palpitation, anemia, lupus erythematosus syndrome, never used alone.

Contraindicated in pt. with coronary-pathy, (اعتلال الشرايين الصغيرة، عندما تتوسع الشرايين) الكبيرة الشرايين الصغيرة مثل الشريان التاجي تنضيق)

May cause angina, MI, coronary spasm.

DRUG-DRUG INTERACTIONS:

1. Thiazide decreases potassium and corticosteroids decreases potassium, using them together leads to increase in hypokalemia.
2. ACEI decreases BP and NSAID increase BP, abolish effect.
3. Methyldopa and antidepressants (imipramine) also abolish effect.
4. Beta blocker and verapamil lead to asystole because verapamil block two sites of vasodilator effect of beta blocker.
5. Alpha blockers and digoxin lead to arrhythmia.

Done by Share and Care 39

هذه الملخصات هي عبارة عن اجتهاد شخصي لمجموعة من طلاب الطب البشري/ عدن معتمدين على ما تم محاضراته او قراءته.. وقد تفيد البعض منكم وللعلم ليس لها أي علاقة مباشرة بأي عضو من أعضاء الهيئة التعليمية في الكلية. زملاننا الأعزاء إن أصبنا فمن الله، وإن أخطأنا فمن أنفسنا ومن الشيطان. نبقى بشرا نخطئ ونصيب لذا يرجى الاشعار في حالة وجود أي ملاحظات عبر ايميل الجروب او في جروبنا على الفيس بوك

(sharencare@outlook.com)